REMARKS

Claims 28, 29, 31, and 36-56 are pending in the application, of which claims 38-56 are currently under consideration. Claims 43, 46, 47, 51, 52, and 56 have been amended. Claims 43, 46, 51, and 56 have each been amended by deleting the word "pharmaceutical" from the preamble of the claim and by deleting the words "pharmaceutically acceptable" from the body of the claim. Claim 47 has been amended by deleting the phrases "at least a portion of" and "wherein the portion is not identical to any portion of Cek5." Claim 52 has been amended by deleting the phrase "at least a portion of."

The undersigned had a telephone conversation with Examiner Brannock on December 17, 2003. The comments below include a statement of the substance of that conversation.

New Issues

Priority

The Examiner alleged that "[a]pplicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120. . . ." Action at page 2. The Examiner stated that the application "must contain a specific reference to the prior application(s) in the first sentence of the specification" and that the specific reference to any nonprovisional application "must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications. . . ." *Id.*

The Divisional Application Transmittal (Transmittal), which was filed on August 23, 1999, requested that the specification be amended by inserting before the first line,

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"This is a division of application Serial No. 08/702,367, filed August 21, 1996, which is a continuation of application Serial No. 08/229,509, filed April 15, 1994. The contents of U.S. Application Serial No. 08/707,367 are being relied upon and are incorporated herein by reference." Transmittal at Box 8. Applicants assert that that amendment complied with the requirements of 37 C.F.R. § 1.78 and therefore the application is entitled to the benefits provided under 35 U.S.C. § 120.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 47-50 under 35 U.S.C. § 112, first paragraph, as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Action at page 3. The Examiner alleged that "[t]he amendment to claim 47 introduces new matter into the specification." *Id.* The Examiner specifically objected to the language "wherein the portion is not identical to any portion of Cek5." *Id.*

Solely to expedite prosecution and without acquiescing to the rejection, applicants have deleted the language "wherein the portion is not identical to any portion of Cek5" from claim 47. Claims 48-50 depend from claim 47. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 47-50 under 35 U.S.C. § 112, first paragraph.

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Objection

The Examiner objected to claims 38-41 because claim 38 allegedly "encompasses several non-elected patentably distinct inventions (Paper 5, 12/19/03); Applicant is required to delete the non-elected inventions of 38(b) and 38(c)." Action at page 4.

Applicants respectfully traverse. In the Restriction Requirement mailed December 19, 2000, the Examiner required restriction to one of six groups, of which applicants elected Group III, "drawn to antibodies, classified in class 530, subclass 388.22." Restriction Requirement at page 2. The Examiner did not require restriction to a single SEQ ID NO within those claims. Rather, the Examiner required an election of a single species, alleging that "[c]laims 1-34 are generic to a plurality of disclosed patentably distinct species comprising SEQ ID NO: 10, 12, 14, and 16. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed." *Id.* at page 3. Applicants elected SEQ ID NO: 10 in the Response filed June 22, 2001.

Applicants respectfully remind the Examiner that, in the event that the elected species is found allowable, the Examiner is required to examine the claims with respect to the non-elected species. See MPEP §809.02(c)(B)(1). The Examiner indicated in a telephone conversation with the undersigned on December 17, 2003, that claims 38-41 would be allowable if the objection is addressed. Thus, because the objection is improper, applicants respectfully request that the Examiner withdraw the objection to claims 38-41 and now examine the non-elected species.

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Outstanding Issues

Drawings

Applicants gratefully acknowledge that the drawings filed February 19, 2003, have been accepted by the Examiner. Action at page 4.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 43, 46, 51, and 56 under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Action at page 5. The Examiner alleged that "[t]he claims require a pharmaceutical composition yet the specification does [*sic*] provide sufficient guidance as to what the antibody is therapeutically effective for; and neither can such a use be reasonably inferred from the prior art, as set forth previously." *Id.* Applicants assume that the Examiner intended to allege that "the specification does *not* provide sufficient guidance as to what the antibody is therapeutically effective for..." and will respond to the rejection accordingly. The Examiner further alleged that "the term 'pharmaceutical composition' implicitly requires that the composition can be used in a therapy or treatment." *Id.*

Solely to expedite prosecution and without acquiescing to the rejection, applicants have deleted the words "pharmaceutical" and "pharmaceutically acceptable" from claims 43, 46, 51, and 56. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 43, 46, 51, and 56 under 35 U.S.C. § 112, first paragraph.

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Rejections under 35 U.S.C. § 102(b)

The Examiner rejected claim 52 under 35 U.S.C. § 102(b) as allegedly being anticipated by Pasquale. Action at page 5. The Examiner alleged that "because [Hek5 and Cek5] are 95% identical, they contain many more of the same 'portions' than those portions that differ between them." Action at page 6.

Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 52 by deleting the phrase "at least a portion of." Thus, claim 52 now recites "[a]n antibody or fragment thereof which is raised against amino acids 1 to 524 of SEQ ID NO: 11."

In order to anticipate a claim, a reference must teach every element of that claim. MPEP § 2131. Applicants assert that Pasquale does not teach amino acids 1 to 524 of SEQ ID NO: 11. Therefore, Pasquale cannot teach an antibody or fragment thereof which is raised against amino acids 1 to 524 of SEQ ID NO: 11.

Applicants respectfully request reconsideration and withdrawal of the rejection of claim 52 under 35 U.S.C. § 102(b) in view of Pasquale.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 42, 44, 45, and 53-54 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Pasquale, as applied to claim 52, in view of U.S. Patent No. 4,816,567 (the '567 patent). Action at page 6. The Examiner alleged that the '567 patent "teaches that in the art of antibody production, monoclonal antibodies

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are generally preferred to polyclonal antibodies, while CDR grafted and otherwise chimeric antibodies are more preferred." *Id.* at pages 6 to 7 (citations omitted).

Applicants respectfully traverse. Applicants will first discuss the rejection with respect to claims 42, 44, and 45. Applicants will then discuss the rejection with respect to claims 53 and 54.

Claim 42 recites "[a] monoclonal antibody or fragment thereof that binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11." Claims 44 and 45 depend from claim 42.

The Examiner alleged that "it would be obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to make a monoclonal, chimeric, or CDR grafted antibodies according to U.S. Patent No. 4816567 when practicing the invention of Pasquale EB." Action at page 7.

Pasquale, however, only discusses the chicken protein Cek5. Applicants assert that if one skilled in the art had made the modification of Pasquale suggested by the Examiner, he would have produced monoclonal, chimeric, or CDR grafted antibodies to the *chicken protein Cek5*, not to the human protein Hek5. Nowhere in Pasquale did the authors teach or suggest the human protein Hek5. Therefore, Pasquale does not teach and would not have suggested an antibody or fragment thereof that "binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11," which is the sequence of the human protein Hek5 (claim 42).

The '567 patent fails to remedy the deficiencies of Pasquale. Therefore, applicants assert that the Examiner failed to establish that the combination of Pasquale and the '567 patent would have suggested monoclonal antibodies or fragments

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according to any of claims 42, 44, and 45. Moreover, applicants need not address the Examiner's contentions concerning the combination of Pasquale and the '567 patent with respect to other elements of certain claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Applicants now address the rejection with respect to claims 53 and 54. Each of those claims depends from claim 52. Solely to expedite prosecution and without acquiescing to the rejection, applicants have amended claim 52 to recite "[a]n antibody or fragment thereof which is raised against amino acids 1 to 524 of SEQ ID NO: 11." Claims 53 and 54 recite the antibody of claim 52 which is a monoclonal antibody or a chimeric antibody, respectively.

For at least the reasons set forth above for the 35 U.S.C. § 102(b) rejection, applicants assert that Pasquale fails to teach and would not have suggested "[a]n antibody or fragment thereof which is raised against amino acids 1 to 524 of SEQ ID NO: 11" (claim 52, from which claims 53 and 54 depend). The '567 patent does not remedy the deficiencies of Pasquale. Thus, applicants assert that the Examiner has failed to establish that the combination of Pasquale and the '567 patent would have suggested every element of claims 53 and 54. Therefore, the Examiner failed to establish that those claims would have been obvious over Pasquale and the '567 patent. Moreover, applicants need not address the Examiner's contentions concerning the combination of Pasquale and the '567 patent with respect to other elements of certain claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

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In conclusion, applicants assert that the Examiner has failed to establish that the combination of Pasquale and the '567 patent would have rendered obvious claims 42, 44, 45, 53 and 54. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Pasquale in view of the '567 patent.

The Examiner rejected claims 42, 44, 45, and 47-50 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Iwase et al. (1993) *Biochem. Biophys. Res Comm.*, 194(2): 698-705 (Iwase) in view of the '567 patent, for the reasons set forth in the Office Action mailed November 18, 2002 (Paper No. 19). Action at page 7. In that Office Action, the Examiner alleged that while Iwase

> do[es] not specifically discuss antibodies to the polypeptides, however it is well appreciated by one of ordinary skill in the art that such antibodies would be useful for diagnosis of gastric cancers as taught by Iwase et al. U.S. Patent No. 4816567 teaches that in the art of antibody production, monoclonal antibodies are generally preferred to polyclonal antibodies, while CDR grafting and otherwise chimeric antibodies are more preferred.

November 18, 2002, Action at page 6.

Applicants incorporate herein by reference the arguments made in the Amendment and Response filed February 19, 2003, at pages 9-11. Briefly, applicants argued that (1) Iwase discusses only upregulation of the H1 mRNA, and not upregulation of the H1 protein, and (2) the Examiner failed to provide a specific factual motivation to combine Iwase and the '567 patent.

In the present Office Action, the Examiner alleged that

> one of skill in the art would read Iwase et al. with the presumption that the polypeptide was also, more likely than not, up regulated as well, and that the primary focus of Iwase et al. is the potential role of the encoded protein and not the mRNA, e.g. in the Introduction (pg 698) Iwase et al. discuss the role of protein kinases in gastric cancers - thus referring to the protein and not to mRNA. The first sentence of the summary indicates

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> that the focus of this plan of research is to find protein tyrosine kinases, identification of mRNAs encoding the kinases being a first step in this process. Regardless, it is readily apparent that one of ordinary skill in the art would be motivated to make antibodies to the protein sequence disclosed by Iwase et al. to study the role of H1 in the development of gastric cancers, e.g., in the potential for diagnosis and/or treatment, as set forth previously.

Action at pages 7 and 8.

Applicants respectfully traverse. Claim 42 recites "[a] monoclonal antibody or fragment thereof that binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11." Claims 44 and 45 depend from claim 42. Claim 47 has been amended to recite "[a]n antibody or fragment thereof which is raised against a polypeptide comprising SEQ ID NO: 11." Claims 48-50 depend from claim 47.

First, the Examiner failed to provide any factual support for the contention that "one of skill in the art would read Iwase et al. with the presumption that the polypeptide was also, more likely than not, up regulated as well." Nowhere in Iwase do the authors assert that the H1 polypeptide is upregulated. Rather, Iwase discusses only the upregulation of the H1 mRNA or the H1 gene. Applicants assert that upregulation of an mRNA or a gene does not necessarily correlate with upregulation of a polypeptide. In fact, Iwase carefully avoids making the statement that the H1 polypeptide itself is upregulated. Instead, he states that "expression of [H1] mRNA was extremely higher in cancer tissues than in normal stomach in all cases examined." Iwase at page 703 (emphasis added).

Furthermore, Iwase discusses a method for detecting the upregulation of H1 mRNA using Northern blot analysis, in which the level of mRNA in a cell is detected using radiolabeled polynucleotide probes. Applicants assert that Northern blot analysis of mRNA is fundamentally different from using an antibody to detect a protein.

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Applicants therefore assert that Iwase does not teach and would not have suggested using antibodies to detect the Hek5 protein.

Applicants assert that the Examiner is obligated to present a factual showing of the teaching or motivation to combine references. The Examiner merely alleged that "it is readily apparent that one of ordinary skill in the art would be motivated to make antibodies to the protein sequence disclosed by Iwase et al. to study the role of H1 in the development of gastric cancers, e.g. in the potential for diagnosis and/or treatment, as set forth previously." Action at page 8.

In reversing the Board of Appeals in *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (2002), the Federal Circuit emphasized that

> our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. . . . This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

Id. at 1343. A copy of the *Lee* case is enclosed.

Thus, the Examiner must identify the specific motivation for combining Iwase and the '567 patent that would have suggested antibodies or fragments thereof that bind to Hek5. Iwase discusses the use of Northern blots to detect upregulation of H1 mRNA in gastric cancers and never suggests the use of antibodies to detect the H1 protein. Applicants assert that the Examiner has failed to identify the specific motivation for combining Iwase and the '567 patent and therefore has failed to set forth a *prima facie* case of obviousness.

Furthermore, applicants assert that Iwase does not teach and would not have suggested a polypeptide comprising SEQ ID NO: 11. SEQ ID NO: 11 is a 970 amino

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acid sequence. Iwase only discusses a polypeptide of about 346 amino acids. Thus, even if the Examiner were able to provide a specific motivation to combine Iwase and the '567 patent, the combination cannot teach and would not have suggested either (1) a monoclonal antibody or fragment thereof that binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11, or (2) an antibody or fragment thereof which is raised against a polypeptide comprising SEQ ID NO: 11. Claims 44 and 45 depend from claim 42 and claims 48-50 depend from claim 47. Thus, for at least the reasons discussed for claims 42 and 47, the combination of Iwase and the '567 patent would not have rendered claims 44, 45, and 48-50 obvious. Moreover, applicants need not address the Examiner's contentions concerning the combination of Iwase and the '567 patent with respect to other elements of certain claims. By not addressing those contentions, applicants in no way acquiesce to those contentions.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 42, 44, 45, and 47-50 under 35 U.S.C. § 103(a) over Iwase in view of the '567 patent.

Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6656 to set up at interview.

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Please grant any extensions of time required to enter this Amendment and Response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: January 9, 2004

By: 

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